



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : <b>A61K 7/48, 31/445</b>	<b>A1</b>	(11) International Publication Number: <b>WO 99/62491</b> (43) International Publication Date: 9 December 1999 (09.12.99)										
<p>(21) International Application Number: PCT/US98/11264</p> <p>(22) International Filing Date: 3 June 1998 (03.06.98)</p> <p>(71) Applicant: GUILFORD PHARMACEUTICALS INC. [US/US]; 6611 Tributary Street, Baltimore, MD 21224 (US).</p> <p>(72) Inventors: HAMILTON, Gregory, S.; 6501 Frederick Road, Catonsville, MD 21228 (US). STEINER, Joseph, P.; 988 Sugar Maple Street, Hampstead, MD 21074 (US).</p> <p>(74) Agent: NATH, Gary, M.; Nath &amp; Associates, 6th floor, 1030 15th Street, N.W., Washington, DC 20005 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>											
<p>(54) Title: SMALL MOLECULE PIPECOLIC ACID DERIVATIVE HAIR GROWTH COMPOSITIONS AND USES</p> <div data-bbox="373 1123 1299 1743"> <p>Promotion of Hair Growth by Neuroimmunophilin Ligands</p> <table border="1"> <thead> <tr> <th>Condition</th> <th>Hair Growth (Relative Index)</th> </tr> </thead> <tbody> <tr> <td>Control</td> <td>1.0</td> </tr> <tr> <td>GPI 1116</td> <td>0.8</td> </tr> <tr> <td>GPI 1206</td> <td>2.0</td> </tr> <tr> <td>F1036</td> <td>2.6</td> </tr> </tbody> </table> <p>0 = no growth 1 = beginning of growth in small tufts 2 = hair growth covering over &lt; 25% of shaved area 3 = hair growth covering over &gt; 25% but less than 50% of shaved area 4 = hair growth covering over &gt; 50% but less than 75% of shaved area 5 = complete hair growth of shaved area</p> </div> <p>(57) Abstract</p> <p>This invention relates to pharmaceutical compositions and methods for treating alopecia and promoting hair growth using pipecolic acid derivatives.</p>			Condition	Hair Growth (Relative Index)	Control	1.0	GPI 1116	0.8	GPI 1206	2.0	F1036	2.6
Condition	Hair Growth (Relative Index)											
Control	1.0											
GPI 1116	0.8											
GPI 1206	2.0											
F1036	2.6											

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

SMALL MOLECULE PIPECOLIC ACID DERIVATIVEHAIR GROWTH COMPOSITIONS AND USES

5 This application is a continuation-in-part of  
U.S. Patent Application No. 08/869,426, filed on June  
4, 1997, the entire contents of which are herein  
incorporated by reference.

BACKGROUND OF THE INVENTION

10

1. Field of Invention

This invention relates to pharmaceutical  
compositions and methods for treating alopecia and  
promoting hair growth using low molecular weight,  
15 small molecule pipecolic acid derivatives.

2. Description of Related Art

Hair loss occurs in a variety of situations.  
These situations include male pattern alopecia,  
20 alopecia senilis, alopecia areata, diseases  
accompanied by basic skin lesions or tumors, and  
systematic disorders such as nutritional disorders and  
internal secretion disorders. The mechanisms causing  
hair loss are very complicated, but in some instances  
25 can be attributed to aging, genetic disposition, the  
activation of male hormones, the loss of blood supply  
to hair follicles, and scalp abnormalities.

The immunosuppressant drugs FK506, rapamycin and  
cyclosporin are well known as potent T-cell specific

immunosuppressants, and are effective against graft rejection after organ transplantation. It has been reported that topical, but not oral, application of FK506 (Yamamoto et al., J. Invest. Dermatol., 1994, 102, 160-164; Jiang et al., J. Invest. Dermatol. 1995, 104, 523-525) and cyclosporin (Iwabuchi et al., J. Dermatol. Sci. 1995, 9, 64-69) stimulates hair growth in a dose-dependent manner. One form of hair loss, alopecia areata, is known to be associated with autoimmune activities; hence, topically administered immunomodulatory compounds are expected to demonstrate efficacy for treating that type of hair loss. The hair growth stimulating effects of FK506 have been the subject of an international patent filing covering FK506 and structures related thereto for hair growth stimulation (Honbo et al., EP 0 423 714 A2). Honbo et al. discloses the use of relatively large tricyclic compounds, known for their immunosuppressive effects, as hair revitalizing agents.

The hair growth and revitalization effects of FK506 and related agents are disclosed in many U.S. patents (Goulet et al., U.S. Patent No. 5,258,389; Luly et al., U.S. Patent No. 5,457,111; Goulet et al., U.S. Patent No. 5,532,248; Goulet et al., U.S. Patent No. 5,189,042; and Ok et al., U.S. Patent No. 5,208,241; Rupprecht et al., U.S. Patent No. 5,284,840; Organ et al., U.S. Patent No. 5,284,877). These patents claim FK506 related compounds. Although

they do not claim methods of hair revitalization, they disclose the known use of FK506 for effecting hair growth. Similar to FK506 (and the claimed variations in the Honbo et al. patent), the compounds claimed in these patents are relatively large. Further, the cited patents relate to immunomodulatory compounds for use in autoimmune related diseases, for which FK506's efficacy is well known.

Other U.S. patents disclose the use of cyclosporin and related compounds for hair revitalization (Hauer et al., U.S. Patent No. 5,342,625; Eberle, U.S. Patent No. 5,284,826; Hewitt et al., U.S. Patent No. 4,996,193). These patents also relate to compounds useful for treating autoimmune diseases and cite the known use of cyclosporin and related immunosuppressive compounds for hair growth.

However, immunosuppressive compounds by definition suppress the immune system and also exhibit other toxic side effects. Accordingly, there is a need for non-immunosuppressant, small molecule compounds which are useful as hair revitalizing compounds.

Hamilton and Steiner disclose in U.S. Patent No. 5,614,547 novel pyrrolidine carboxylate compounds which bind to the immunophilin FKBP12 and stimulate nerve growth, but which lack immunosuppressive effects. Unexpectedly, it has been discovered that

these non-immunosuppressant compounds promote hair growth with an efficacy similar to FK506. Yet their novel small molecule structure and non-immunosuppressive properties differentiate them from FK506 and related immunosuppressive compounds found in the prior art.

#### SUMMARY OF THE INVENTION

The present invention relates to a method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of a low molecular weight, small molecule pipecolic acid derivative.

The present invention further relates to a pharmaceutical composition which comprises:

- (i) an effective amount of a pipecolic acid derivative for treating alopecia or promoting hair growth in an animal; and
- (ii) a pharmaceutically acceptable carrier.

The pipecolic acid derivatives used in the inventive methods and pharmaceutical compositions include immunosuppressive and non-immunosuppressive compounds having an affinity for FKBP-type immunophilins, particularly FKBP12. Non-immunosuppressive compounds, as their name suggests, do not exert any significant immunosuppressive activity.

### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a photograph of mice treated with a vehicle after six weeks. FIG. 1 shows that less than 3% of the shaved area is covered with new hair growth when the vehicle (control) is administered.

FIG. 2 is a photograph of mice treated with 10  $\mu$ M of GPI 1044 after six weeks. FIG. 2 shows that 90% of the shaved area is covered with new hair growth when GPI 1044 is administered.

FIG. 3 is a bar graph plotting the hair growth scores of unshaven animals and shaven animals treated with a vehicle, GPI 1044 (1  $\mu$ M, 3  $\mu$ M and 10  $\mu$ M), and related pipicollic acid derivative neuroimmunophilin FKBP ligands GPI 1116 (1  $\mu$ M and 10  $\mu$ M) and GPI 1102 (1  $\mu$ M and 3  $\mu$ M).

FIG. 4 is a bar graph depicting the relative hair growth indices for C57 Black 6 mice treated with a vehicle, FK506, and related neuroimmunophilin FKBP ligands 14 days after treatment with each identified compound. Figure 4 demonstrates the remarkable early hair growth promoted by neuroimmunophilin FKBP ligands.

### DETAILED DESCRIPTION OF THE INVENTION

25

#### Definitions

"Alopecia" refers to deficient hair growth and partial or complete loss of hair, including without limitation androgenic alopecia (male pattern

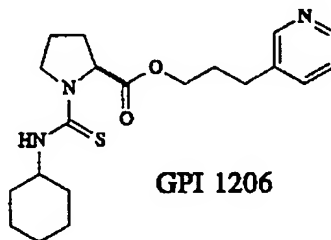
baldness), toxic alopecia, alopecia senilis, alopecia areata, alopecia pelada and trichotillomania. Alopecia results when the pilar cycle is disturbed. The most frequent phenomenon is a shortening of the hair growth or anagen phase due to cessation of cell proliferation. This results in an early onset of the catagen phase, and consequently a large number of hairs in the telogen phase during which the follicles are detached from the dermal papillae, and the hairs fall out. Alopecia has a number of etiologies, including genetic factors, aging, local and systemic diseases, febrile conditions, mental stresses, hormonal problems, and secondary effects of drugs.

"GPI 1044" refers to Compound 4.

"GPI 1102" refers to 4-phenyl-1-(3-phenylpropyl) butyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate.

"GPI 1116" refers to 1-phenethyl-3-phenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate.

"GPI 1206" refers to a compound of formula



GPI 1206



"Isomers" refer to different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. "Enantiomers" are a pair of  
5 stereoisomers that are non-superimposable mirror images of each other. "Diastereoisomers" are stereoisomers which are not mirror images of each other. "Racemic mixture" means a mixture containing equal parts of individual enantiomers. "Non-racemic  
10 mixture" is a mixture containing unequal parts of individual enantiomers or stereoisomers.

"Pharmaceutically acceptable salt, ester, or solvate" refers to a salt, ester, or solvate of a subject compound which possesses the desired  
15 pharmacological activity and which is neither biologically nor otherwise undesirable. A salt, ester, or solvate can be formed with inorganic acids such as acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate,  
20 citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, gluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-  
25 hydroxyethanesulfonate, lactate, maleate, methanesulfonate, naphthylate, 2-naphthalenesulfonate, nicotinate, oxalate, sulfate, thiocyanate, tosylate and undecanoate. Examples of base salts, esters, or

solvates include ammonium salts; alkali metal salts, such as sodium and potassium salts; alkaline earth metal salts, such as calcium and magnesium salts; salts with organic bases, such as dicyclohexylamine salts; N-methyl-D-glucamine; and salts with amino acids, such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quarternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl, and diamyl sulfates; long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides; aralkyl halides, such as benzyl and phenethyl bromides; and others. Water or oil-soluble or dispersible products are thereby obtained.

"Pilar cycle" refers to the life cycle of hair follicles, and includes three phases:

- (1) the anagen phase, the period of active hair growth which, insofar as scalp hair is concerned, lasts about three to five years;
- (2) the catagen phase, the period when growth stops and the follicle atrophies which, insofar as scalp hair is concerned, lasts about one to two weeks; and
- (3) the telogen phase, the rest period when hair progressively separates and finally falls

out which, insofar as scalp hair is concerned, lasts about three to four months.

Normally 80 to 90 percent of the follicles are in the anagen phase, less than 1 percent being in the catagen phase, and the rest being in the telogen phase. In the telogen phase, hair is uniform in diameter with a slightly bulbous, non-pigmented root. By contrast, in the anagen phase, hair has a large colored bulb at its root.

"Promoting hair growth" refers to maintaining, inducing, stimulating, accelerating, or revitalizing the germination of hair.

"Treating alopecia" refers to:

(i) preventing alopecia in an animal which may be predisposed to alopecia; and/or

(ii) inhibiting, retarding or reducing alopecia; and/or

(iii) promoting hair growth; and/or

(iv) prolonging the anagen phase of the hair cycle; and/or

(v) converting vellus hair to growth as terminal hair. Terminal hair is coarse, pigmented, long hair in which the bulb of the hair follicle is seated deep in the dermis. Vellus hair, on the other hand, is fine, thin, non-pigmented short hair in which the hair bulb is located superficially in the dermis. As alopecia progresses, the hairs change from the terminal to the vellus type.

### Methods of the Present Invention

The present invention relates to a method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal  
5 an effective amount of a pipecolic acid derivative.

The inventive method is particularly useful for treating male pattern alopecia, alopecia senilis, alopecia areata, alopecia resulting from skin lesions or tumors, alopecia resulting from cancer therapy such  
10 as chemotherapy and radiation, and alopecia resulting from systematic disorders such as nutritional disorders and internal secretion disorders.

### Pharmaceutical Compositions of the Present Invention

15 The present invention also relates to a pharmaceutical composition comprising:

- (i) an effective amount of a pipecolic acid derivative for treating alopecia or promoting hair growth in an animal; and
- 20 (ii) a pharmaceutically acceptable carrier.

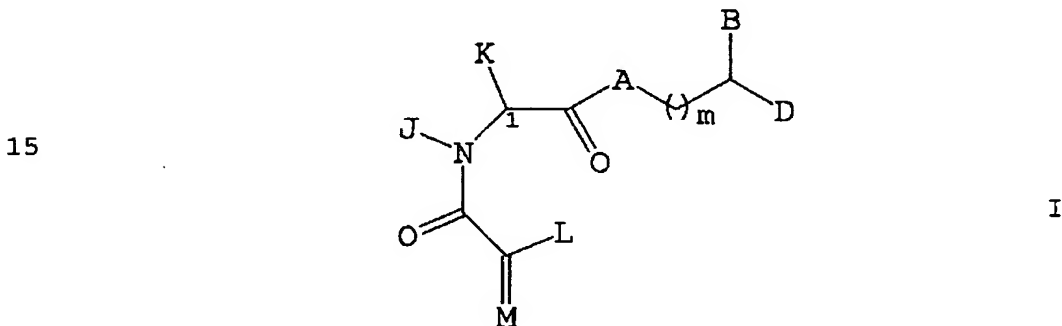
### PIPECOLIC ACID DERIVATIVES

The pipecolic acid derivatives used in the methods and pharmaceutical compositions of the present  
25 invention are low molecular weight, small molecule compounds having an affinity for FKBP-type immunophilins, such as FKBP12. When a pipecolic acid derivative binds to an FKBP-type immunophilin, it has

been found to inhibit the prolyl-peptidyl *cis-trans*-isomerase, or rotamase, activity of the binding protein. Unexpectedly, the compounds have also been found to stimulate hair growth. These rotamase  
 5 inhibiting compounds may be immunosuppressive or non-immunosuppressive. Examples of useful compounds are set forth below.

# FORMULA I

10 An exemplary pipecolic acid derivative is a compound of formula I



20 or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

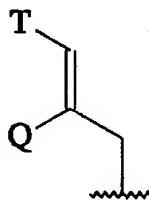
$m$  is 0-3;

$A$  is  $\text{CH}_2$ ,  $\text{O}$ ,  $\text{NH}$ , or  $\text{N}-(\text{C}_1-\text{C}_4 \text{ alkyl})$ ;

25  $B$  and  $D$  are independently  $\text{Ar}$ ,  $\text{C}_5-\text{C}_7$  cycloalkyl substituted  $\text{C}_1-\text{C}_6$  straight or branched chain alkyl or  $\text{C}_2-\text{C}_6$  straight or branched chain alkenyl,  $\text{C}_5-\text{C}_7$  cycloalkenyl substituted  $\text{C}_1-\text{C}_6$  straight or branched chain alkyl or  $\text{C}_2-\text{C}_6$  straight or branched chain

alkenyl, or Ar substituted C<sub>1</sub>-C<sub>6</sub> straight or branched-chain alkyl or C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, wherein in each case, one or two carbon atom(s) of said alkyl or alkenyl may be substituted  
5 with one or two heteroatom(s) independently selected from the group consisting of oxygen, sulfur, SO, and SO<sub>2</sub> in chemically reasonable substitution patterns, or

10



15

wherein Q is hydrogen, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, or C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl; and

20

T is Ar or C<sub>5</sub>-C<sub>7</sub> cycloalkyl substituted at positions 3 and 4 with substituents independently selected from the group consisting of hydrogen, hydroxy, O-(C<sub>1</sub>-C<sub>4</sub> alkyl), O-(C<sub>2</sub>-C<sub>4</sub> alkenyl), and carbonyl;

25

Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl, monocyclic and bicyclic heterocyclic ring systems with individual ring sizes being 5 or 6 which contain in either or both rings a total of 1-4 heteroatom(s) independently selected from the group consisting of oxygen, nitrogen and sulfur; wherein Ar contains 1-3

substituent(s) independently selected from the group consisting of hydrogen, halo, hydroxy, hydroxymethyl, nitro,  $\text{CF}_3$ , trifluoromethoxy,  $\text{C}_1\text{-C}_6$  straight or branched chain alkyl,  $\text{C}_2\text{-C}_6$  straight or branched chain alkenyl, O- ( $\text{C}_1\text{-C}_4$  straight or branched chain alkyl), O- ( $\text{C}_2\text{-C}_4$  straight or branched chain alkenyl), O-benzyl, O-phenyl, amino, 1,2-methylenedioxy, carbonyl, and phenyl;

L is either hydrogen or U; M is either oxygen or CH-U, provided that if L is hydrogen, then M is CH-U, or if M is oxygen then L is U;

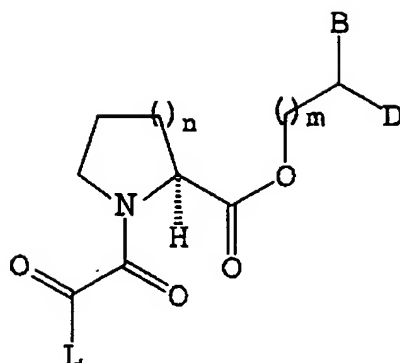
U is hydrogen, O- ( $\text{C}_1\text{-C}_4$  straight or branched chain alkyl), O- ( $\text{C}_2\text{-C}_4$  straight or branched chain alkenyl),  $\text{C}_1\text{-C}_6$  straight or branched chain alkyl,  $\text{C}_2\text{-C}_6$  straight or branched chain alkenyl,  $\text{C}_5\text{-C}_7$  cycloalkyl,  $\text{C}_5\text{-C}_7$  cycloalkenyl substituted with  $\text{C}_1\text{-C}_4$  straight or branched chain alkyl or  $\text{C}_2\text{-C}_4$  straight or branched chain alkenyl, ( $\text{C}_1\text{-C}_4$  alkyl or  $\text{C}_2\text{-C}_4$  alkenyl)-Ar, or Ar;

J is hydrogen,  $\text{C}_1$  or  $\text{C}_2$  alkyl, or benzyl; K is  $\text{C}_1\text{-C}_4$  straight or branched chain alkyl, benzyl or cyclohexylmethyl; or J and K are taken together to form a 5-7 membered heterocyclic ring which is substituted with oxygen, sulfur, SO, or  $\text{SO}_2$ ; and

said pipecolic acid derivative has an affinity for FKBP-type immunophilins.

Representative species of Formula I are presented in Table I.

TABLE I



10

Compound	n	m	B	D	L
1	2	0	3-Phenyl-propyl	3-(3-Pyridyl)-propyl	Phenyl
15	2	0	3-Phenyl-propyl	3-(2-Pyridyl)-propyl	Phenyl
20	2	0	3-Phenyl-propyl	2-(4-Methoxy-phenyl)ethyl	Phenyl
25	2	0	3-Phenyl-propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl
30	2	0	3-Phenyl-propyl	2-(3-Pyridyl)-propyl	3,4,5-Trimethoxyphenyl
35	2	0	3-Phenyl-propyl	3-(2-Pyridyl)-propyl	3,4,5-Trimethoxyphenyl

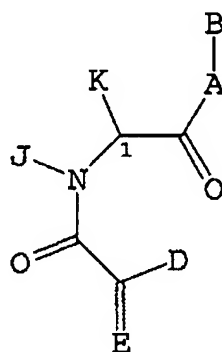


TABLE I (continued)

5	Compound	n	m	B	D	L
10	8	2	0	3-Phenyl-propyl	3-(4-Methoxy-phenyl)propyl	3,4,5-Trimethoxyphenyl
15	9	2	0	3-Phenyl-propyl	3-(3-Pyridyl)-propyl	3-Iso-propoxy-phenyl

FORMULA II

U.S. Patent No. 5,330,993, incorporated herein by reference, discloses an exemplary pipecolic acid  
 20 derivative of Formula II



II

25

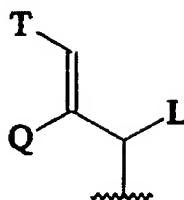
or a pharmaceutically acceptable salt, ester, or  
 30 solvate thereof, wherein:

A is O, NH, or N-(C<sub>1</sub>-C<sub>4</sub> alkyl);

B is hydrogen, CHL-Ar, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, C<sub>5</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, Ar substituted C<sub>1</sub>-

16

C<sub>6</sub> alkyl or C<sub>2</sub>-C<sub>6</sub> alkenyl, or



wherein L and Q are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, or C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl; and

T is Ar or C<sub>5</sub>-C<sub>7</sub> cyclohexyl substituted at positions 3 and 4 with substituents independently selected from the group consisting of hydrogen, hydroxy, O-(C<sub>1</sub>-C<sub>4</sub> alkyl), O-(C<sub>2</sub>-C<sub>4</sub> alkenyl), and carbonyl;

Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl having 1-3 substituent(s) independently selected from the group consisting of hydrogen, halo, hydroxy, nitro, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, O-(C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl), O-(C<sub>2</sub>-C<sub>4</sub> straight or branched chain alkenyl), O-benzyl, O-phenyl, amino, and phenyl.

D is hydrogen or U; E is oxygen or CH-U, provided that if D is hydrogen, then E is CH-U, or if E is oxygen, then D is U;

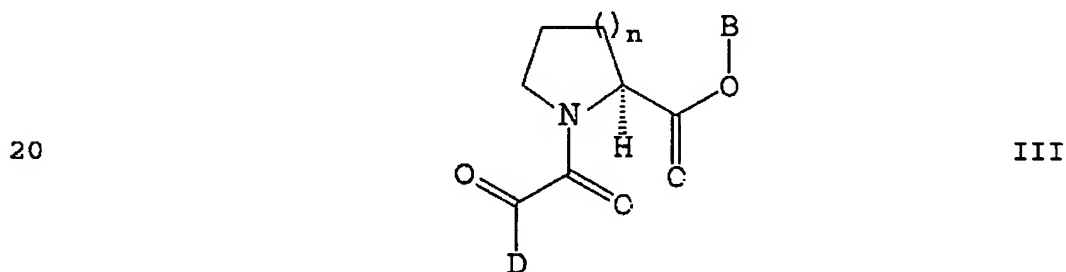
U is hydrogen, O-(C<sub>1</sub>-C<sub>4</sub> straight or branched chain

alkyl), O-(C<sub>2</sub>-C<sub>4</sub> straight or branched chain alkenyl), C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, C<sub>5</sub>-C<sub>7</sub>-cycloalkyl, C<sub>5</sub>-C<sub>7</sub>-cycloalkenyl substituted with C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl or C<sub>2</sub>-C<sub>4</sub> straight or branched chain alkenyl, 2-indolyl, 3-indolyl, (C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>2</sub>-C<sub>4</sub> alkenyl)-Ar, or Ar;

J is hydrogen, C<sub>1</sub> or C<sub>2</sub> alkyl, or benzyl; K is C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl, benzyl or cyclohexylethyl; or J and K are taken together to form a 5-7 membered heterocyclic ring which is substituted with oxygen, sulfur, SO, or SO<sub>2</sub>.

### FORMULA III

A preferred pipecolic acid derivative is a compound of Formula III



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

n is 2;

D is phenyl, methoxy, 2-furyl, or 3,4,5-trimethoxyphenyl; and

B is benzyl, 3-phenylpropyl, 4-(4-methoxyphenyl)butyl, 4-phenylbutyl, phenethyl, 3-cyclohexylpropyl, 4-cyclohexylbutyl, 3-cyclopentylpropyl, 4-cyclohexylbutyl, 3-phenoxybenzyl,  
5 3-(3-indolyl)propyl, or 4-(4-methoxyphenyl)butyl;

provided that:

when D is phenyl, then B is benzyl, 3-phenylpropyl, 4-(4-methoxyphenyl)butyl, 4-phenylbutyl, phenethyl, or 4-cyclohexylbutyl;

10 when D is methoxy, B is benzyl, 4-cyclohexylbutyl, 3-cyclohexylpropyl, or 3-cyclopentylpropyl;

when D is 2-furyl, then B is benzyl; and

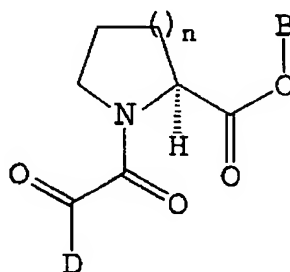
when D is 3,4,5-trimethoxyphenyl, then B is  
15 4-cyclohexylbutyl, 3-phenoxybenzyl, 4-phenylbutyl, 3-(3-indolyl)propyl, or 4-(4-methoxyphenyl)butyl.

Representative species of Formula III are  
presented in Table II.

20

TABLE II

25



III

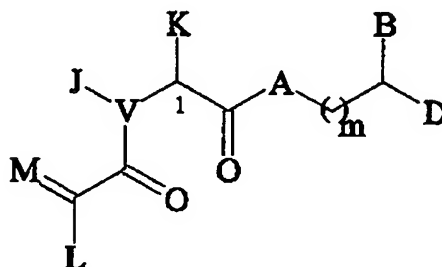
TABLE II (continued)

	Compound	B	D	n
5	10	Benzyl	Phenyl	2
	11	3-Phenylpropyl	Phenyl	2
10	12	4-(4-Methoxyphenyl)- butyl	Phenyl	2
	13	4-Phenylbutyl	Phenyl	2
15	14	Phenethyl	Phenyl	2
	15	4-Cyclohexylbutyl	Phenyl	2
	16	Benzyl	Methoxy	2
20	17	4-Cyclohexylbutyl	Methoxy	2
	18	3-Cyclohexylpropyl	Methoxy	2
25	19	3-Cyclopentylpropyl	Methoxy	2
	20	Benzyl	2-Furyl	2
	21	4-Cyclohexylbutyl	3,4,5- Trimethoxyphenyl	2
30	22	3-Phenoxybenzyl	3,4,5- Trimethoxyphenyl	2
35	23	4-Phenylbutyl	3,4,5- Trimethoxyphenyl	2
	24	3-(3-Indolyl)propyl	3,4,5- Trimethoxyphenyl	2
40	25	4-(4-Methoxyphenyl)- butyl	3,4,5- Trimethoxyphenyl	2

FORMULA IV

The pipecolic acid derivative may also be a compound of formula IV

5



IV

10

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

V is C, N, or S;

15

J and K, taken together with V and the carbon atom to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to V, one or more heteroatom(s) selected from the group consisting of O, S, SO, SO<sub>2</sub>, N, NH, and NR;

20

R is either C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>5</sub>-C<sub>6</sub> cycloalkenyl, or Ar<sub>1</sub>, wherein R is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>2</sub>-C<sub>4</sub> alkenyloxy, phenoxy,

25

benzyloxy, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar<sub>2</sub>;

Ar<sub>1</sub> and Ar<sub>2</sub> are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or  
5 heterocyclic ring; wherein the individual ring size is 5-8 members; wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S;

A, B, D, L, M, and m are as defined in Formula I  
10 above; and

said pipecolic acid derivative has an affinity for FKBP-type immunophilins.

All the compounds of Formulas I-IV possess asymmetric centers and thus can be produced as  
15 mixtures of stereoisomers or as individual R- and S-stereoisomers. The individual stereoisomers may be obtained by using an optically active starting material, by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage  
20 of the synthesis, or by resolving the compounds of Formulas I-IV. It is understood that the compounds of Formulas I-IV encompass individual stereoisomers as well as mixtures (racemic and non-racemic) of stereoisomers. Preferably, S-stereoisomers are used  
25 in the pharmaceutical compositions and methods of the present invention.

Affinity for FKBP12

The compounds used in the inventive methods and pharmaceutical compositions have an affinity for the FK506 binding protein, particularly FKBP12. The inhibition of the prolyl peptidyl *cis-trans* isomerase activity of FKBP may be measured as an indicator of this affinity.

K<sub>i</sub> Test Procedure

Inhibition of the peptidyl-prolyl isomerase (rotamase) activity of the compounds used in the inventive methods and pharmaceutical compositions can be evaluated by known methods described in the literature (Harding et al., *Nature*, 1989, 341:758-760; Holt et al. *J. Am. Chem. Soc.*, 115:9923-9938). These values are obtained as apparent K<sub>i</sub>'s and are presented for representative compounds in TABLE III.

The *cis-trans* isomerization of an alanine-proline bond in a model substrate, N-succinyl-Ala-Ala-Pro-Phe-p-nitroanilide, is monitored spectrophotometrically in a chymotrypsin-coupled assay, which releases para-nitroanilide from the *trans* form of the substrate. The inhibition of this reaction caused by the addition of different concentrations of inhibitor is determined, and the data is analyzed as a change in first-order rate constant as a function of inhibitor concentration to yield the apparent K<sub>i</sub> values.



In a plastic cuvette are added 950 mL of ice cold assay buffer (25 mM HEPES, pH 7.8, 100 mM NaCl), 10 mL of FKBP (2.5 mM in 10 mM Tris-Cl pH 7.5, 100 mM NaCl, 1 mM dithiothreitol), 25 mL of chymotrypsin (50 mg/mL in 1 mM HCl) and 10 mL of test compound at various concentrations in dimethyl sulfoxide. The reaction is initiated by the addition of 5 mL of substrate (succinyl-Ala-Phe-Pro-Phe-para-nitroanilide, 5 mg/mL in 2.35 mM LiCl in trifluoroethanol).

The absorbance at 390 nm versus time is monitored for 90 seconds using a spectrophotometer and the rate constants are determined from the absorbance versus time data files.

TABLE III

## In Vitro Test Results - Formulas I-III

	Compound	K <sub>i</sub> ( $\mu$ M)
5	10	1.5
	13	0.35
	14	1.1
	15	0.4
10	16	80
	17	6
	18	20
	19	35
	20	3
15	21	0.04
	22	0.018
	23	0.019
	24	0.017
	25	0.013

20

Route of Administration

To effectively treat alopecia or promote hair growth, the compounds used in the inventive methods and pharmaceutical compositions must readily affect the targeted areas. For these purposes, the compounds are preferably administered topically to the skin.

25

For topical application to the skin, the compounds can be formulated into suitable ointments containing the compounds suspended or dissolved in,

for example, mixtures with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water.

5 Alternatively, the compounds can be formulated into suitable lotions or creams containing the active compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl ester  
10 wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Other routes of administration known in the pharmaceutical art are also contemplated by this invention.

15

#### Dosage

Dosage levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with  
20 preferred levels of about 0.1 mg to about 1,000 mg. The specific dose level for any particular patient will vary depending upon a variety of factors, including the activity of the specific compound employed; the age, body weight, general health, sex  
25 and diet of the patient; the time of administration; the rate of excretion; drug combination; the severity of the particular disease being treated; and the form of administration. Typically, in vitro dosage-effect

results provide useful guidance on the proper doses for patient administration. Studies in animal models are also helpful. The considerations for determining the proper dose levels are well known in the art.

5           The compounds can be administered with other hair revitalizing agents. Specific dose levels for the other hair revitalizing agents will depend upon the factors previously stated and the effectiveness of the drug combination.

10

#### EXAMPLES

The following examples are illustrative of the present invention and are not intended to be limitations thereon. Unless otherwise indicated, all percentages are based upon 100% by weight of the final composition.

15

#### Example 1

##### In Vivo Hair Generation Tests With C57 Black 6 Mice

20           Experiment A: C57 black 6 mice were used to demonstrate the hair revitalizing properties of pipecolic acid derivative GPI 1044 (compound 4), as well as related pipecolic acid derivative neuroimmunophilin FKBP ligands GPI 1102 and GPI 1116.

25           C57 black 6 mice, approximately 7 weeks old, had an area of about 2 inches by 2 inches on their hindquarters shaved to remove all existing hair. Care was taken not to nick or cause abrasion to the

underlying dermal layers. The animals were in anagen growth phase, as indicated by the pinkish color of the skin. Referring now to FIGS. 1 and 2, four animals were treated by topical administration with 20% propylene glycol vehicle (FIG. 1), and seven animals were treated by topical administration with 10  $\mu$ M GPI 1044 (FIG. 2). The animals were treated with vehicle or GPI 1044 every 48 hours (3 applications total over the course of 5 days) and the hair growth was allowed to proceed for 6 weeks. Hair growth was quantitated by the percent of shaved area covered by new hair growth during this time period.

FIG. 1 shows that animals treated with vehicle exhibited only a small amount of hair growth in patches or tufts, with less than 3% of the shaved area covered with new growth. In contrast, FIGS. 2 shows that animals treated with 10  $\mu$ M GPI 1044 exhibited dramatic hair growth, covering as much as 50% of the shaved area in some animals. FIG. 3 compares the hair growth score of unshaven animals with the hair growth scores of shaven animals treated with a vehicle and GPI 1044 (1  $\mu$ M, 3  $\mu$ M and 10  $\mu$ M), as well as related neuroimmunophilin FKBP ligands GPI 1116 (1  $\mu$ M and 10  $\mu$ M) and GPI 1102 (1  $\mu$ M and 3  $\mu$ M).

Experiment B: C57 Black 6 mice were used to demonstrate the hair revitalizing properties of neuroimmunophilin FKBP ligands. C57 Black 6 mice, 55 to 75 days old, had an area of about 2 inches by 2

inches on their hindquarters shaved to remove all existing hair. Care was taken not to nick or cause abrasion to the underlying dermal layers. The animals were in a anagen growth phase when shaved. Five  
5 animals per group were treated by topical administration with a vehicle, FK506, or a neuroimmunophilin FKBP ligand (GPI 1116 or 1206) at a concentration of one micromole per milliliter to the shaved area. The animals were treated three times per  
10 week, and hair growth was evaluated 14 days after initiation of treatment. Hair growth was quantitated by the percent of shaved area covered by new hair growth, as scored by a blinded observer, on a scale of 0 (no growth) to five (complete hair regrowth in  
15 shaved area).

Figure 4 shows that after 14 days, the animals treated with vehicle exhibited the beginning of growth in small tufts. In contrast, animals treated with one of the low molecular weight, small molecule, neuro-  
20 immunophilin FKBP ligands exhibited dramatic hair growth.

Example 2

A lotion comprising the following composition may be prepared.

5		(%)
	95% Ethanol	80.0
	a pipecolic acid derivative as defined above	10.0
	$\alpha$ -Tocopherol acetate	0.01
10	Ethylene oxide (40 mole) adducts of hardened castor oil	0.5
	purified water	9.0
	perfume and dye	q.s.

Into 95% ethanol are added a pipecolic acid derivative,  $\alpha$ -tocopherol acetate, ethylene oxide (40 mole) adducts of hardened castor oil, perfume and a dye. The resulting mixture is stirred and dissolved, and purified water is added to the mixture to obtain a transparent liquid lotion.

5 ml of the lotion may be applied once or twice per day to a site having marked baldness or alopecia.

Example 3

A lotion comprising the following composition shown may be prepared.

5		(%)
	95% Ethanol	80.0
	a pipecolic acid derivative as defined above	0.005
	Hinokitol	0.01
10	Ethylene oxide (40 mole) adducts of hardened castor oil	0.5
	Purified water	19.0
	Perfume and dye	q.s.

Into 95% ethanol are added a pipecolic acid derivative, hinokitol, ethylene oxide (40 mole) adducts of hardened castor oil, perfume, and a dye. The resulting mixture is stirred, and purified water is added to the mixture to obtain a transparent liquid lotion.

The lotion may be applied by spraying once to 4 times per day to a site having marked baldness or alopecia.



Example 4

An emulsion may be prepared from A phase and B phase having the following compositions.

5	(A phase)	(%)
	Whale wax	0.5
	Cetanol	2.0
	Petrolatum	5.0
	Squalane	10.0
10	Polyoxyethylene (10 mole) monostearate	2.0
	Sorbitan monooleate	1.0
	a pipecolic acid derivative as defined above	0.01
	(B phase)	(%)
	Glycerine	10.0
15	Purified water	69.0
	Perfume, dye, and preservative	q.s.

The A phase and the B phase are respectively heated and melted and maintained at 80°C. Both phases are then mixed and cooled under stirring to normal temperature to obtain an emulsion.

The emulsion may be applied by spraying once to four times per day to a site having marked baldness or alopecia.

Example 5

A cream may be prepared from A phase and B phase having the following compositions.

5	(A Phase)	(%)
	Fluid paraffin	5.0
	Cetostearyl alcohol	5.5
	Petrolatum	5.5
	Glycerine monostearate	33.0
10	Polyoxyethylene (20 mole) 2-octyldodecyl ether	3.0
	Propylparaben	0.3
	(B Phase)	(%)
	a picecolic acid derivative as defined above	0.8
15	Glycerine	7.0
	Dipropylene glycol	20.0
	Polyethylene glycol 4000	5.0
	Sodium Hexametaphosphate	0.005
20	Purified water	44.895

The A phase is heated and melted, and maintained at 70°C. The B phase is added into the A phase and the mixture is stirred to obtain an emulsion. The emulsion is then cooled to obtain a cream.

25 The cream may be applied once to 4 times per day to a site having marked baldness or alopecia.

Example 6

A liquid comprising the following composition may be prepared.

5		(%)
	Polyoxyethylene butyl ether	20.0
	Ethanol	50.0
	a pipecolic acid derivative as defined above	0.001
	Propylene glycol	5.0
10	Polyoxyethylene hardened castor oil derivative (ethylene oxide 80 mole adducts)	0.4
	Perfume	q.s.
	Purified water	q.s.

15           Into ethanol are added polyoxypropylene butyl ether, propylene glycol, polyoxyethylene hardened castor oil, a pipecolic acid derivative, and perfume. The resulting mixture is stirred, and purified water is added to the mixture to obtain a liquid.

20           The liquid may be applied once to 4 times per day to a site having marked baldness or alopecia.

Example 7

A shampoo comprising the following composition may be prepared.

5		(%)
	Sodium laurylsulfate	5.0
	Triethanolamine laurylsulfate	5.0
	Betaine lauryldimethylaminoacetate	6.0
	Ethylene glycol distearate	2.0
10	Polyethylene glycol	5.0
	a pipecolic acid derivative as defined above	5.0
	Ethanol	2.0
	Perfume	0.3
15	Purified water	69.7

Into 69.7 of purified water are added 5.0 g of sodium laurylsulfate, 5.0 g of triethanolamine laurylsulfate, 6.0 g of betaine lauryldimethylaminoacetate. Then a mixture obtained by adding 5.0 g of a pipecolic acid derivative, 5.0 g of polyethylene glycol, and 2.0 g of ethylene glycol distearate to 2.0 g of ethanol, followed by stirring, and 0.3 g of perfume are successively added. The resulting mixture is heated and subsequently cooled to obtain a shampoo.

The shampoo may be used on the scalp once or twice per day.

Example 8

A patient is suffering from alopecia senilis. A  
pipecolic acid derivative, or a pharmaceutical  
composition comprising the same, may be administered  
5 to the patient. Increased hair growth is expected to  
occur following treatment.

Example 9

A patient is suffering from male pattern  
10 alopecia. A pipecolic acid derivative, or a  
pharmaceutical composition comprising the same, may be  
administered to the patient. Increased hair growth is  
expected to occur following treatment.

Example 10

A patient is suffering from alopecia areata. A  
pipecolic acid derivative, or a pharmaceutical  
composition comprising the same, may be administered  
to the patient. Increased hair growth is expected to  
15 occur following treatment.

Example 11

A patient is suffering from hair loss caused by  
skin lesions. A pipecolic acid derivative, or a  
25 pharmaceutical composition comprising the same, may be  
administered to the patient. Increased hair growth is  
expected to occur following treatment.

Example 12

A patient is suffering from hair loss caused by tumors. A pipecolic acid derivative, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 13

A patient is suffering from hair loss caused by a systematic disorder, such as a nutritional disorder or an internal secretion disorder. A pipecolic acid derivative, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 14

A patient is suffering from hair loss caused by chemotherapy. A pipecolic acid derivative, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 15

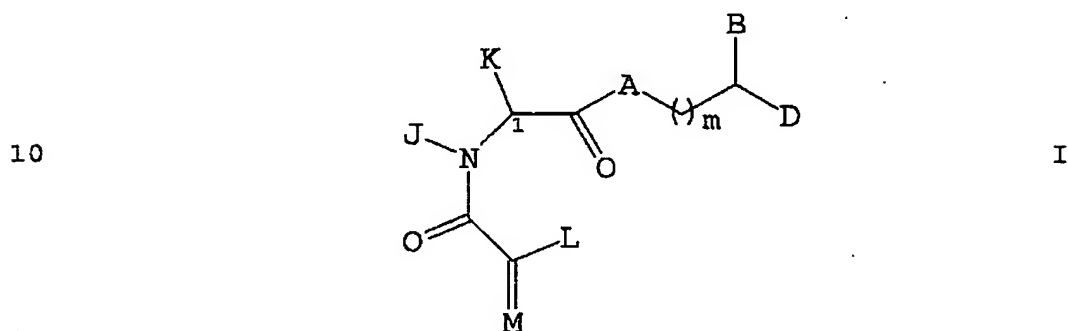
A patient is suffering from hair loss caused by radiation. A pipecolic acid derivative, or a pharmaceutical composition comprising the same, may be

administered to the patient. Increased hair growth is expected to occur following treatment.

5       The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

## WE CLAIM:

1. A method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of a  
 5 pipecolic acid derivative of formula I

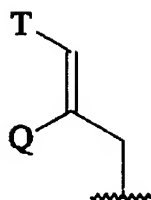


- or a pharmaceutically acceptable salt, ester, or  
 15 solvate thereof, wherein:

A is CH<sub>2</sub>, O, NH, or N-(C<sub>1</sub>-C<sub>4</sub> alkyl);

- B and D are independently Ar, C<sub>5</sub>-C<sub>7</sub> cycloalkyl substituted C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl or C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl substituted C<sub>1</sub>-C<sub>6</sub> straight or branched  
 20 chain alkyl or C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, or Ar substituted C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl or C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, wherein in each case, one or two carbon  
 25 atom(s) of said alkyl or alkenyl may be substituted with one or two heteroatom(s) independently selected from the group consisting of oxygen, sulfur, SO, and SO<sub>2</sub> in chemically reasonable substitution patterns, or





5

wherein Q is hydrogen, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl or C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl; and

10 T is Ar or C<sub>5</sub>-C<sub>7</sub> cycloalkyl substituted at positions 3 and 4 with substituents independently selected from the group consisting of hydrogen, hydroxy, O-(C<sub>1</sub>-C<sub>4</sub> alkyl), O-(C<sub>2</sub>-C<sub>4</sub> alkenyl), and carbonyl;

15 Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl, monocyclic and bicyclic heterocyclic ring systems with individual ring sizes being 5 or 6 which contain in  
20 either or both rings a total of 1-4 heteroatoms independently selected from oxygen, nitrogen and sulfur; wherein Ar contains 1-3 substituent(s) independently selected from the group consisting of hydrogen, halo, hydroxy, hydroxymethyl, nitro, CF<sub>3</sub>,  
25 trifluoromethoxy, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, O-(C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl), O-(C<sub>2</sub>-C<sub>4</sub> straight or branched chain alkenyl), O-benzyl, O-phenyl, amino,

1,2-methylenedioxy, carbonyl, and phenyl;

L is either hydrogen or U; M is either oxygen or CH-U, provided that if L is hydrogen, then M is CH-U, or if M is oxygen then L is U;

5 U is hydrogen, O-(C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl), O-(C<sub>2</sub>-C<sub>4</sub> straight or branched chain alkenyl), C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, C<sub>5</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl substituted with C<sub>1</sub>-C<sub>4</sub> straight or  
10 branched chain alkyl or C<sub>2</sub>-C<sub>4</sub> straight or branched chain alkenyl, (C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>2</sub>-C<sub>4</sub> alkenyl)-Ar, or Ar;

J is hydrogen, C<sub>1</sub> or C<sub>2</sub> alkyl, or benzyl; K is C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl, benzyl or cyclohexylmethyl; or J and K are taken together to  
15 form a 5-7 membered heterocyclic ring which is substituted with oxygen, sulfur, SO, or SO<sub>2</sub>;

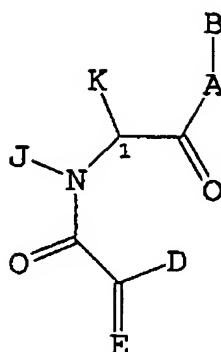
n is 0-3; and

said pipecolic acid derivative has an affinity for FKBP-type immunophilins.

20

2. A method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of a pipecolic acid derivative of formula II

41



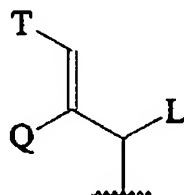
II

5

or a pharmaceutically acceptable salt, ester, or  
 10 solvate thereof, wherein:

A is O, NH, or N-(C<sub>1</sub>-C<sub>4</sub> alkyl);

B is hydrogen, CHL-Ar, C<sub>1</sub>-C<sub>6</sub> straight or branched  
 chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl,  
 C<sub>5</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, Ar substituted C<sub>1</sub>-  
 15 C<sub>6</sub> alkyl or C<sub>2</sub>-C<sub>6</sub> alkenyl, or



20

wherein L and Q are independently  
 hydrogen, C<sub>1</sub>-C<sub>6</sub> straight or branched chain  
 alkyl, or C<sub>2</sub>-C<sub>6</sub> straight or branched chain  
 alkenyl; and

25

T is Ar or C<sub>5</sub>-C<sub>7</sub> cyclohexyl substituted  
 at positions 3 and 4 with substituents  
 independently selected from the group  
 consisting of hydrogen, hydroxy, O-(C<sub>1</sub>-C<sub>4</sub>

alkyl), O-(C<sub>2</sub>-C<sub>4</sub> alkenyl), and carbonyl;

Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl having 1-3  
5 substituent(s) independently selected from the group consisting of hydrogen, halo, hydroxy, nitro, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, O-(C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl), O-(C<sub>2</sub>-C<sub>4</sub> straight or branched chain  
10 alkenyl), O-benzyl, O-phenyl, amino, and phenyl.

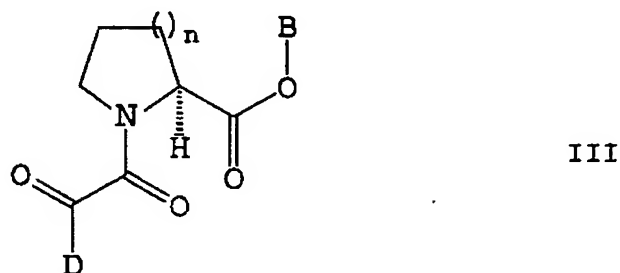
D is hydrogen or U; E is oxygen or CH-U, provided that if D is hydrogen, then E is CH-U, or if E is oxygen, then D is U;

U is hydrogen, O-(C<sub>1</sub>-C<sub>4</sub> straight or branched chain  
15 alkyl), O-(C<sub>2</sub>-C<sub>4</sub> straight or branched chain alkenyl), C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, C<sub>5</sub>-C<sub>7</sub>-cycloalkyl, C<sub>5</sub>-C<sub>7</sub>-cycloalkenyl substituted with C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl or C<sub>2</sub>-C<sub>4</sub> straight or branched  
20 chain alkenyl, 2-indolyl, 3-indolyl, (C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>2</sub>-C<sub>4</sub> alkenyl)-Ar, or Ar;

J is hydrogen, C<sub>1</sub> or C<sub>2</sub> alkyl, or benzyl; K is C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl, benzyl or cyclohexylethyl; or J and K are taken together to form  
25 a 5-7 membered heterocyclic ring which is substituted with oxygen, sulfur, SO, or SO<sub>2</sub>.

3. A method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of a pipecolic acid derivative of formula III

5



10

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

n is 2;

15 D is phenyl, methoxy, 2-furyl, or 3,4,5-trimethoxyphenyl; and

B is benzyl, 3-phenylpropyl, 4-(4-methoxyphenyl)butyl, 4-phenylbutyl, phenethyl, 3-cyclohexylpropyl, 4-cyclohexylbutyl, 3-cyclopentylpropyl, 4-cyclohexylbutyl, 3-phenoxybenzyl,  
20 3-(3-indolyl)propyl, or 4-(4-methoxyphenyl)butyl;

provided that

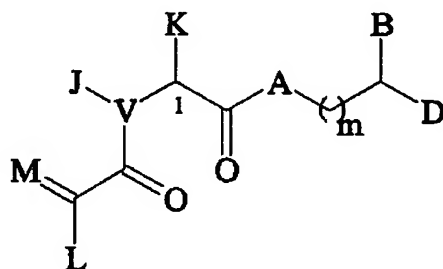
when D is phenyl, then B is benzyl, 3-phenylpropyl, 4-(4-methoxyphenyl)butyl, 4-phenylbutyl, phenethyl, or 4-cyclohexylbutyl;  
25

when D is methoxy, then B is benzyl, 4-cyclohexylbutyl, 3-cyclohexylpropyl, or 3-cyclopentylpropyl;

when D is 2-furyl, then B is benzyl; and

when D is 3,4,5-trimethoxyphenyl, then B is  
4-cyclohexylbutyl, 3-phenoxybenzyl, 4-  
phenylbutyl, 3-(3-indolyl)propyl, or 4-(4-  
methoxyphenyl)butyl.

4. A method for treating alopecia or promoting  
hair growth in an animal, which comprises  
administering to said animal an effective amount of a  
pipecolic acid derivative of formula IV



IV

or a pharmaceutically acceptable salt, ester, or  
solvate thereof, wherein:

V is C, N, or S;

J and K, taken together with V and the carbon  
atom to which they are respectively attached, form a  
5-7 membered saturated or unsaturated heterocyclic  
ring containing, in addition to V, one or more  
heteroatom(s) selected from the group consisting of O,  
S, SO, SO<sub>2</sub>, N, NH, and NR;

R is either C<sub>1</sub>-C<sub>9</sub> straight or branched chain  
alkyl, C<sub>2</sub>-C<sub>9</sub> straight or branched chain alkenyl, C<sub>3</sub>-C<sub>9</sub>,

cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, or Ar<sub>1</sub>, wherein R is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>2</sub>-C<sub>4</sub> alkenyloxy, phenoxy, benzyloxy, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar<sub>2</sub>;

Ar<sub>1</sub> and Ar<sub>2</sub> are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring; wherein the individual ring size is 5-8 members; wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S;

A, B, D, L, M, and m are as defined in claim 1 above; and

said pipecolic acid derivative has an affinity for FKBP-type immunophilins.

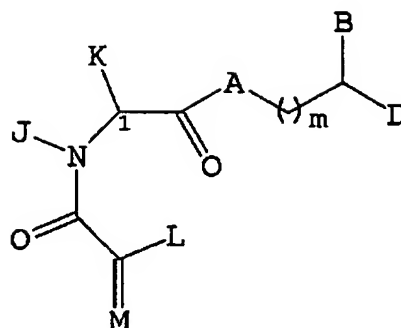
20

5. A pharmaceutical composition which comprises:

(i) an effective amount of a pipecolic acid derivative for treating alopecia or promoting hair growth in an animal, wherein the pipecolic acid derivative is a compound of formula I

46

5

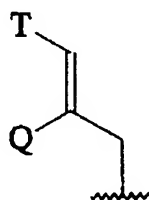


10 or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A is  $\text{CH}_2$ , O, NH, or N-( $\text{C}_1$ - $\text{C}_4$  alkyl);

15 B and D are independently Ar,  $\text{C}_5$ - $\text{C}_7$  cycloalkyl substituted  $\text{C}_1$ - $\text{C}_6$  straight or branched chain alkyl or  $\text{C}_2$ - $\text{C}_6$  straight or branched chain alkenyl,  $\text{C}_5$ - $\text{C}_7$  cycloalkenyl substituted  $\text{C}_1$ - $\text{C}_6$  straight or branched chain alkyl or  $\text{C}_2$ - $\text{C}_6$  straight or branched chain alkenyl, or Ar substituted  $\text{C}_1$ - $\text{C}_6$  straight or branched chain alkyl or  $\text{C}_2$ - $\text{C}_6$  straight or branched chain alkenyl, wherein in each case, one or two carbon atom(s) of said alkyl or alkenyl may be substituted with one or two heteroatom(s) independently selected from the group consisting of oxygen, sulfur, SO, and  $\text{SO}_2$  in chemically reasonable substitution patterns, or

25





wherein Q is hydrogen, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl or C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl; and

5 T is Ar or C<sub>5</sub>-C<sub>7</sub> cycloalkyl substituted at positions 3 and 4 with substituents independently selected from the group consisting of hydrogen, hydroxy, O-(C<sub>1</sub>-C<sub>4</sub> alkyl), O-(C<sub>2</sub>-C<sub>4</sub> alkenyl), and carbonyl;

10 Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl, monocyclic and bicyclic heterocyclic ring systems with individual ring sizes being 5 or 6 which contain in either or both rings a total of 1-4 heteroatoms  
15 independently selected from oxygen, nitrogen and sulfur; wherein Ar contains 1-3 substituent(s) independently selected from the group consisting of hydrogen, halo, hydroxy, hydroxymethyl, nitro, CF<sub>3</sub>, trifluoromethoxy, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, O-(C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl), O-(C<sub>2</sub>-C<sub>4</sub> straight or branched chain alkenyl), O-benzyl, O-phenyl, amino, 1,2-methylenedioxy, carbonyl, and phenyl;  
20

L is either hydrogen or U; M is either oxygen or  
25 CH-U, provided that if L is hydrogen, then M is CH-U, or if M is oxygen then L is U;

U is hydrogen, O-(C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl), O-(C<sub>2</sub>-C<sub>4</sub> straight or branched chain alkenyl),

C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, C<sub>5</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl substituted with C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl or C<sub>2</sub>-C<sub>4</sub> straight or branched chain alkenyl, (C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>2</sub>-C<sub>4</sub> alkenyl)-Ar, or Ar;

J is hydrogen, C<sub>1</sub> or C<sub>2</sub> alkyl, or benzyl; K is C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl, benzyl or cyclohexylmethyl; or J and K are taken together to form a 5-7 membered heterocyclic ring which is substituted with oxygen, sulfur, SO, or SO<sub>2</sub>;

n is 0-3; and

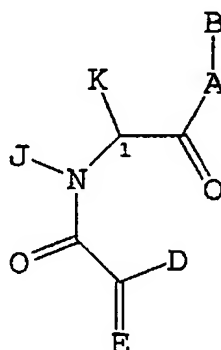
said pipecolic acid derivative has an affinity for FKBP-type immunophilins; and

(ii) a pharmaceutically acceptable carrier.

15

6. A pharmaceutical composition which comprises:

(i) an effective amount of a pipecolic acid derivative for treating alopecia or promoting hair growth in an animal, wherein the pipecolic acid derivative is a compound of formula II



II

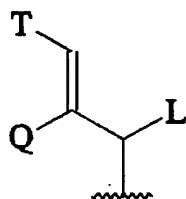
25

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A is O, NH, or N-(C<sub>1</sub>-C<sub>4</sub> alkyl);

5 B is hydrogen, CHL-Ar, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, C<sub>5</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, Ar substituted C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>2</sub>-C<sub>6</sub> alkenyl, or

10



15

wherein L and Q are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, or C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl; and

20

T is Ar or C<sub>5</sub>-C<sub>7</sub> cyclohexyl substituted at positions 3 and 4 with substituents independently selected from the group consisting of hydrogen, hydroxy, O-(C<sub>1</sub>-C<sub>4</sub> alkyl), O-(C<sub>2</sub>-C<sub>4</sub> alkenyl), and carbonyl,

25

Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl having 1-3 substituent(s) independently selected from the group consisting of hydrogen, halo, hydroxy, nitro, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, O-(C<sub>1</sub>-C<sub>4</sub> straight or branched

chain alkyl), O-(C<sub>2</sub>-C<sub>4</sub> straight or branched chain alkenyl), O-benzyl, O-phenyl, amino, and phenyl.

D is hydrogen or U; E is oxygen or CH-U, provided that if D is hydrogen, then E is CH-U, or if E is oxygen, then D is U;

U is hydrogen, O-(C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl), O-(C<sub>2</sub>-C<sub>4</sub> straight or branched chain alkenyl), C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl, C<sub>5</sub>-C<sub>7</sub>-cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl substituted with C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl or C<sub>2</sub>-C<sub>4</sub> straight or branched chain alkenyl, 2-indolyl, 3-indolyl, (C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>2</sub>-C<sub>4</sub> alkenyl)-Ar, or Ar;

J is hydrogen, C<sub>1</sub> or C<sub>2</sub> alkyl, or benzyl; K is C<sub>1</sub>-C<sub>4</sub> straight or branched chain alkyl, benzyl or cyclohexylethyl; or J and K are taken together to form a 5-7 membered heterocyclic ring which is substituted with oxygen, sulfur, SO, or SO<sub>2</sub>; and

(ii) a pharmaceutically acceptable carrier.

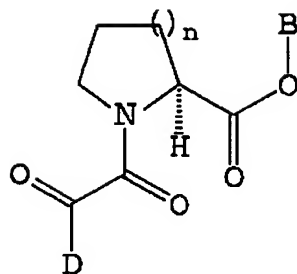
20

7. A pharmaceutical composition which comprises:

(i) an effective amount of a pipecolic acid derivative for treating alopecia or promoting hair growth in an animal, wherein the pipecolic acid derivative is a compound of formula III

25

51



III

5

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

10

n is 2;

D is phenyl, methoxy, 2-furyl, or 3,4,5-trimethoxyphenyl; and

15

B is benzyl, 3-phenylpropyl, 4-(4-methoxyphenyl)butyl, 4-phenylbutyl, phenethyl, 3-cyclohexylpropyl, 4-cyclohexylbutyl, 3-cyclopentylpropyl, 4-cyclohexylbutyl, 3-phenoxybenzyl, 3-(3-indolyl)propyl, or 4-(4-methoxyphenyl)butyl;

provided that

20

when D is phenyl, then B is benzyl, 3-phenylpropyl, 4-(4-methoxyphenyl)butyl, 4-phenylbutyl, phenethyl, or 4-cyclohexylbutyl;

when D is methoxy, then B is benzyl, 4-cyclohexylbutyl, 3-cyclohexylpropyl, or 3-cyclopentylpropyl;

25

when D is 2-furyl, then B is benzyl; and

when D is 3,4,5-trimethoxyphenyl, then B is 4-cyclohexylbutyl, 3-phenoxybenzyl, 4-phenylbutyl, 3-(3-indolyl)propyl, or 4-(4-

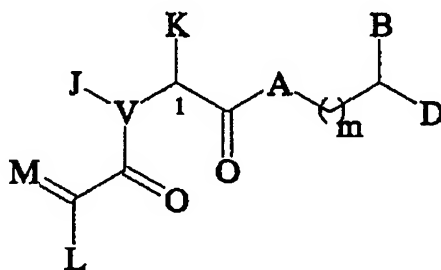
methoxyphenyl)butyl; and

(ii) a pharmaceutically acceptable carrier.

8. A pharmaceutical composition which  
5 comprises:

(i) an effective amount of a pipecolic acid  
derivative for treating alopecia or promoting hair  
growth in an animal, wherein the pipecolic acid  
derivative is a compound of formula formula IV

10



IV

15

or a pharmaceutically acceptable salt, ester, or  
solvate thereof, wherein:

V is C, N, or S;

20 J and K, taken together with V and the carbon  
atom to which they are respectively attached, form a  
5-7 membered saturated or unsaturated heterocyclic  
ring containing, in addition to V, one or more  
heteroatom(s) selected from the group consisting of O,  
25 S, SO, SO<sub>2</sub>, N, NH, and NR;

R is either C<sub>1</sub>-C<sub>9</sub> straight or branched chain  
alkyl, C<sub>2</sub>-C<sub>9</sub> straight or branched chain alkenyl, C<sub>3</sub>-C<sub>9</sub>  
cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, or Ar<sub>1</sub>, wherein R is

either unsubstituted or substituted with one or more  
substituent(s) independently selected from the group  
consisting of halo, haloalkyl, carbonyl, carboxy,  
hydroxy, nitro, trifluoromethyl, C<sub>1</sub>-C<sub>6</sub> straight or  
5 branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain  
alkenyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>2</sub>-C<sub>4</sub> alkenyloxy, phenoxy,  
benzyloxy, thioalkyl, alkylthio, sulfhydryl, amino,  
alkylamino, aminoalkyl, aminocarboxyl, and Ar<sub>2</sub>;

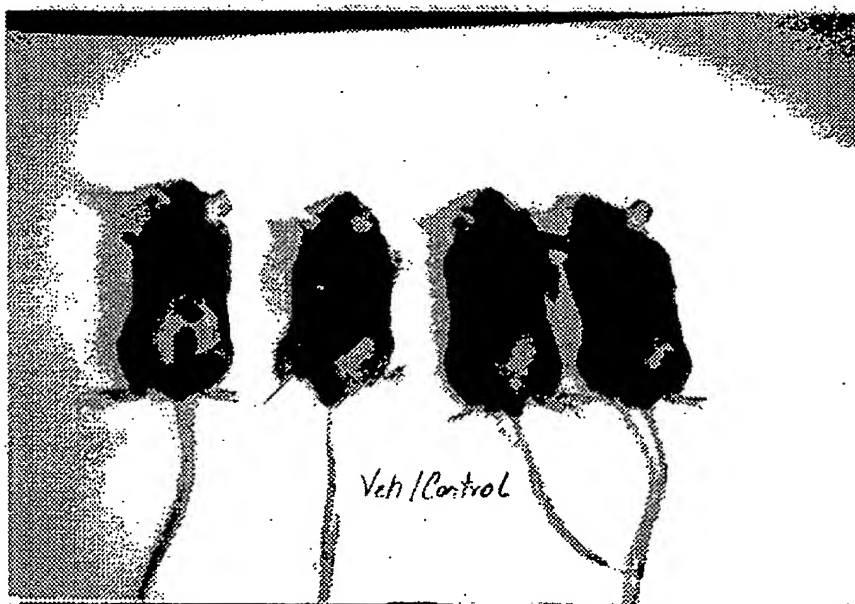
Ar<sub>1</sub> and Ar<sub>2</sub> are independently an alicyclic or  
10 aromatic, mono-, bi- or tricyclic, carbo- or  
heterocyclic ring; wherein the individual ring size is  
5-8 members; wherein said heterocyclic ring contains  
1-6 heteroatom(s) independently selected from the  
group consisting of O, N, and S;

15 A, B, D, L, M, and m are as defined in claim 5  
above; and

(ii) a pharmaceutically acceptable carrier.

1 / 4

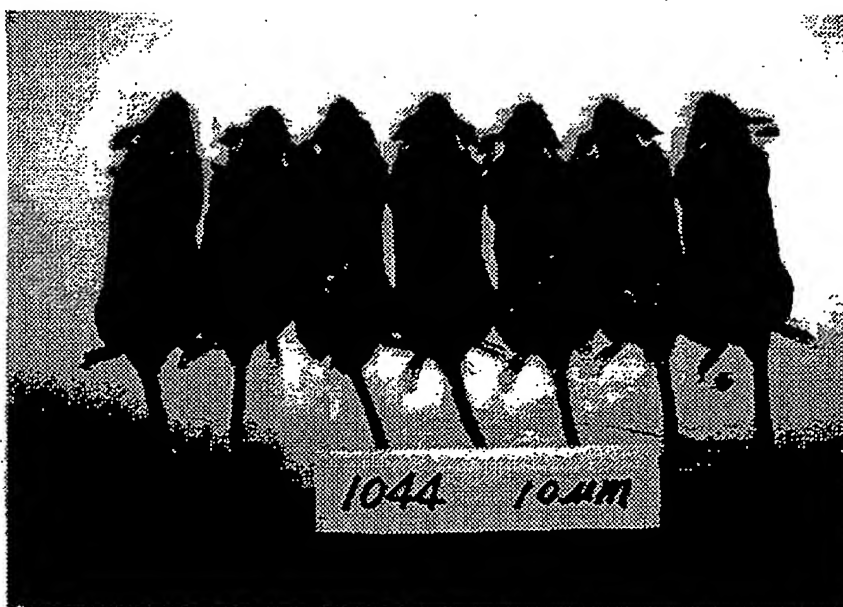
FIG. 1



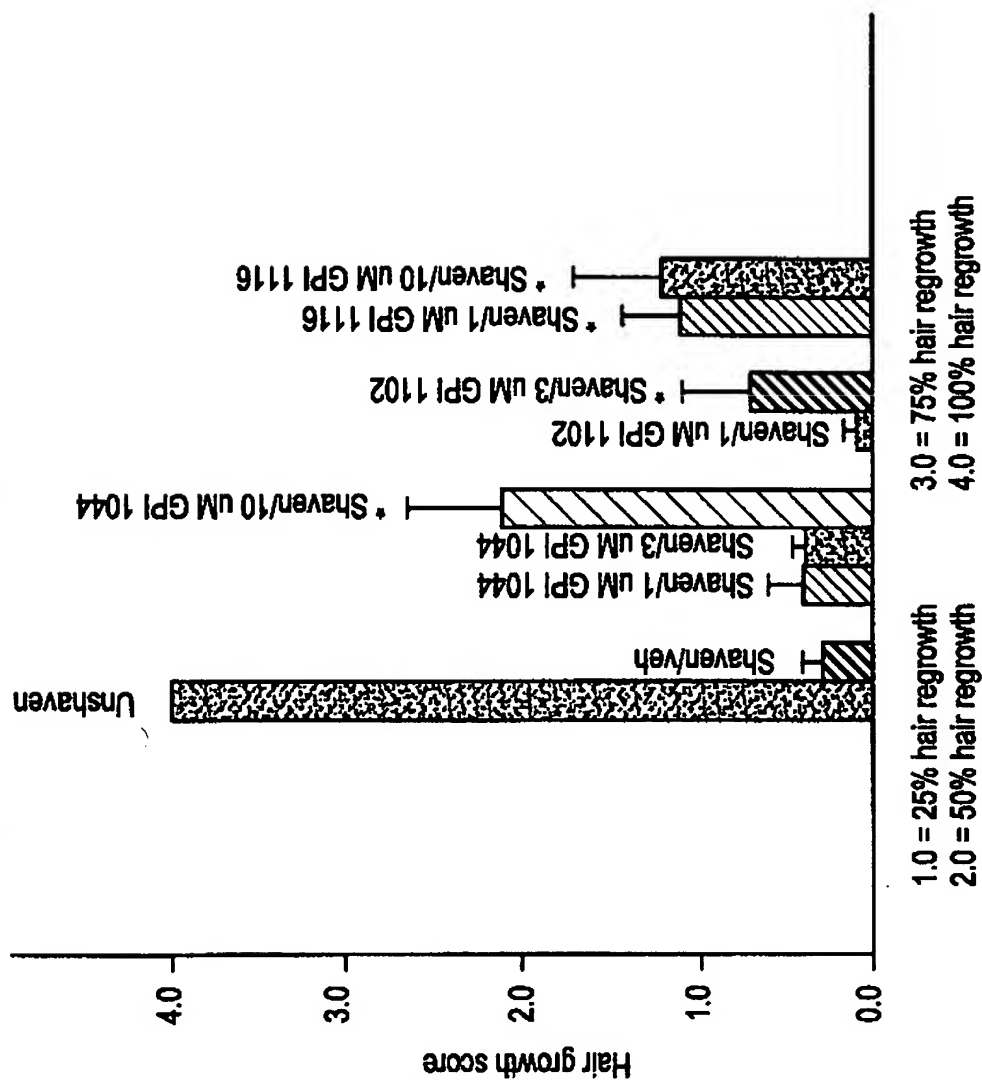


2 / 4

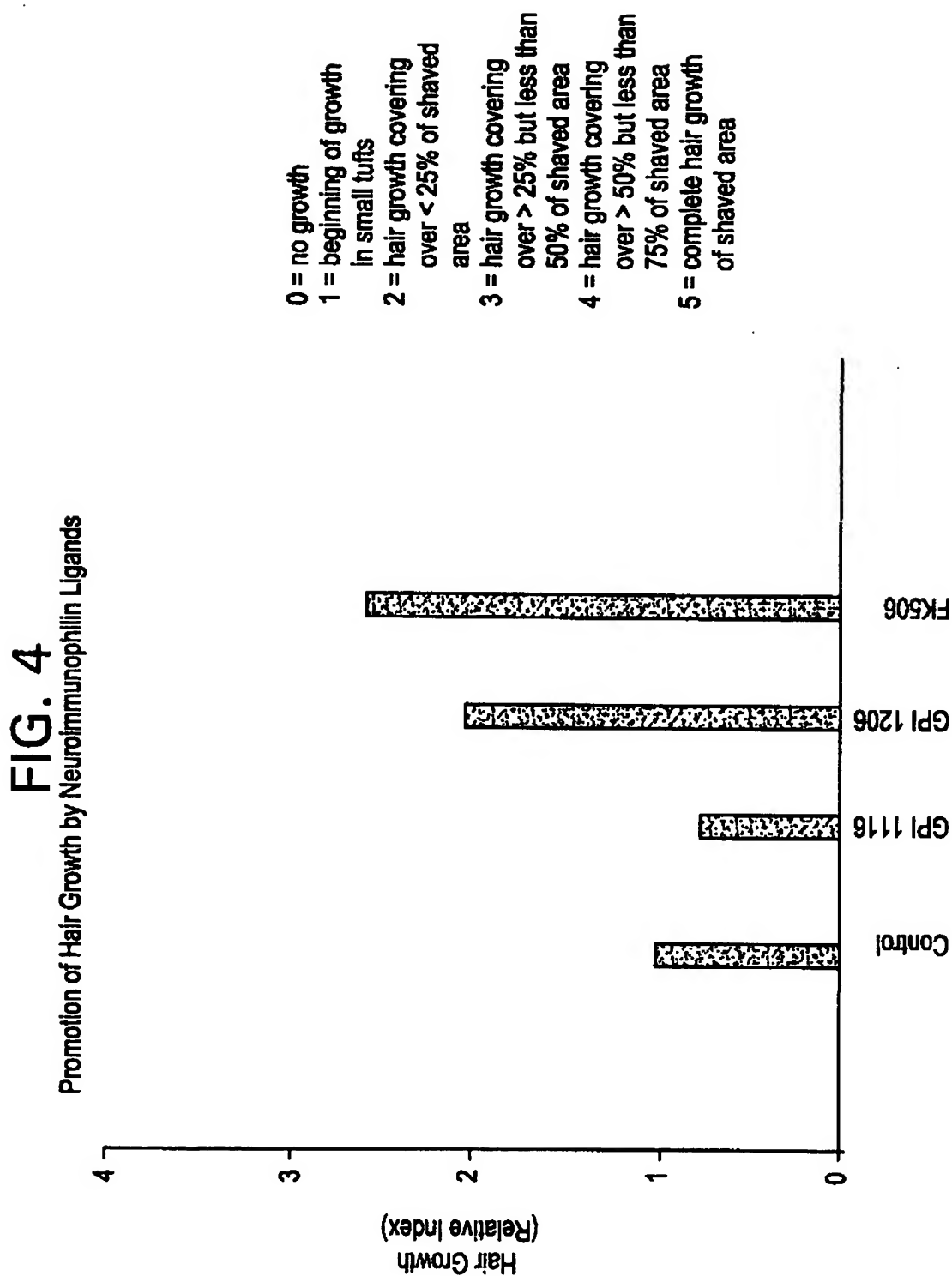
FIG.2



**FIG. 3**  
Promotion of Hair Growth by GPI Neuroimmunophilin Ligands



4 / 4



# INTERNATIONAL SEARCH REPORT

Int. Patent Application No.  
PCT/US 98/11264

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K7/48 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 423 714 A (FUJISAWA PHARM. CO., LTD) 24 April 1991 cited in the application see the whole document ---	1-8
P, X	WO 98 13343 A (GUILFORD PHARM. INC.) 2 April 1998 see the whole document -----	5-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

13 October 1998

Date of mailing of the international search report

21/10/1998

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Glikman, J-F

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 11264

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 1-8 (PARTIAL)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
In view of the large number of compounds which are defined by the wording of the claims, the search has been performed on the general idea and compounds mentioned in the examples of the description.
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/11264

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 423714 A	24-04-1991	AT 107499 T	15-07-1994
		CA 2027608 A	17-04-1991
		DE 69010139 D	28-07-1994
		DE 69010139 T	13-10-1994
		DK 423714 T	25-07-1994
		JP 3204807 A	06-09-1991
		US 5215995 A	01-06-1993
WO 9813343 A	02-04-1998	US 5786378 A	28-07-1998
		AU 4259097 A	17-04-1998

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☒ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**